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LD50 PREDICTION OF CONDENSED AZOLE DERIVATIVES USING MICROCOSM ADMET

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Condensed azole derivatives, benzimidazoles and imidazopyrimidines are privileged structures and are a wide range of different types of pharmacological activity [1]. A preliminary assessment in silico of acute toxicity of condensed azoles is an important task in a directed search for highly active and at the same time low toxic congeners.

The goal was to evaluate the acute toxicity of condensed azole derivatives with the method of similarity with the program Microcosm ADMET.

In the experiment on mice after intraperitoneal injection was determined by the values of LD50 372 new derivatives of condensed azoles. Database structure and acute toxicity of these substances were randomly divided into a training sample (300 compounds) and test sample (72 compounds). The program is implemented as a Microcosm of ADMET predictive algorithm.

1. The chemical structures of the training and test samples are translated into descriptors of the specialized language QL [2].
2. 2. For the predicted compounds are calculated values of QL-modified Tanimoto similarity coefficient TQL [3] to each connection vector.
3. Selected compounds of the training set, with TQL>0.7.
4. The LD50 values of selected compounds are calculated as evaluation of acute toxicity prediction join: median, 95% confidence interval for the median, arithmetic mean, standard error, toxicity class, the average of the similarities.

To assess the reliability of the method was performed prediction of toxicity for 72compounds of test samples, and conducted correlation analysis between the experimental LD50 values and their estimates.

Nonparametric Spearman correlation coefficient with the experimental data was as follows: median assessment $R_{Sp}=0.463$, $p=4.2\cdot10^{-5}$; for the average of $RSp=0.340$, $p=3.5\cdot10^{-3}$.

Median and average estimates of toxicity are correlated very well together: $R_{Sp}=0.833$, $p<1.0\cdot10^{-6}$.

Thus, when predicting the acute toxicity of condensed azole derivatives with the method of similarity using the program Microcosm ADMET a median estimate more accurate than the arithmetic mean. However, both these estimates are reasonably accurate and can be used together.

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